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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LY, CHEYNE D	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 01/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/816,755	VAIDEHI ET AL.	
	Examiner	Art Unit	
	Cheyne D Ly	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57* is/are pending in the application.

4a) Of the above claim(s) *2 and 4-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3 and 35-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-57* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/08/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' arguments filed March 08, 2004 have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

2. The withdrawal of claims 2 and 4-34, and addition of claims 35-57 have been acknowledged.

3. Claims 1, 3, and 35-57 are examined on the merits.

4. NON-FINAL OFFICE ACTION.

OJBECTIONS

5. Claim 3 is objected to because said claim does not end with a period due to the period previously present has been lined through. Appropriate correction is required.

6. Claim 55 is objected to because spacing is needed in the term "100ps" in line 2. Appropriate correction is required.

CLAIM REJECTIONS - 35 U.S.C. § 112, FIRST PARAGRAPH

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 3, and 35-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in

the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

9. NEW MATTER REJECTION.

10. Claim 1, recites the method directed to "a membrane-bound protein having a plurality of helical regions" which has not been found in the instant specification. It is noted that the claimed method is specific to a method for "predicting the structure of a membrane-bound protein having a plurality of α-helical regions" which is different from the generic requirement of "plurality of helical regions".

11. Claim 1, lines 4-6, the limitation of "identifying two or more ranges of amino acids in the amino acid sequence" has not been found in the specification. The same issue is present in claims 3, 37-39, and 41. It is noted Applicant points page 12, lines 16-23, and page 18, line 22 to page 19, line 3 to support the amendment in claim 37. However, the disclosure of "the modeling of any transmembrane protein having one or more membrane-spanning α-helices" is different from the new limitation of "two or more ranges of amino acids in the amino acid sequence."

12. Claim 46, lines 2-3, recites the limitation of "effect of the environment of the membrane-bound protein" which is different from the disclosure of specific parameters on page 14, lines 5-9, as pointed to by Applicant. It is noted the generic limitation of "environment" is different from the specific limitations such as temperature and pressure pointed to by Applicant.

13. Claims 56 and 57 recite limitations that have not been found in the pointed to support. For example, the pointed to support, page 19, lines 3-7, discloses "modeling the structure of

having a relatively large number (e.g. about 4 or more) membrane-spanning helical regions, such as seven-helical GPCR's", which is different from the limitation of "four or more helices" of claim 56, or "seven or more helices" of claim 57.

CLAIM REJECTIONS - 35 U.S.C. § 112, SECOND PARAGRAPH

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 47 and 49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

16. Claim 47, line 3, recites the limitation of "charges for the transmembrane protein" which causes said claim to be vague and indefinite because it is not clear whether said limitation is directed to the "membrane-bound protein" or "the transmembrane regions" in independent claim 1. Claim 47 is vague and indefinite because it is not clear whether "the transmembrane protein" is distinct from the "membrane-bound protein". The same issue is present in claim 49.

CLAIM REJECTIONS - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 1, 36-38, 41, 42, 44-46, 48, and 51-57 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Biggin et al. (1999).

19. Biggin et al. discloses computer method simulations predicting membrane bound proteins comprising a plurality of α-helix (Abstract et al.), as in instant claim 1, lines 1-3.

20. Biggin et al. provides amino acid sequences for said membrane-bound proteins wherein bacteriorhodopsin has as set 7 helices comprising transmembrane regions. It is noted that in Table 1 "[o]nly the sequence of the TM helix is given, even though simulations included the entire sequence (page 169, Table 1), as in instant claim 1, lines 4-7, and claim 37.

21. Biggin et al. discloses using mean-field membrane simulations (first simulation) to provide a useful means to obtain information about possible conformations and/or orientations of a protein (pages 166-170, §§6.1 to 6.2), as in instant claim 1, lines 8-9.

22. Biggin et al. discloses, in the all atom simulations (page 170, §7), TM helix bundle models may be constructed by less costly simulations without bilayer, then refined (optimize) by subsequent (second simulation etc.) MD simulations in an atomistic bilayer or bilayer-mimetic environment. The membrane-mimetic environment has been used in two MD simulations of ion channels formed by bundles of α-helices. These helices had evolved into a coiled-coil (loop) tetrametric structure with a left handed twist (page 172, column 1, lines 3-28). Fluctuations in the structure over the course of the simulation were greater for inter-helix loops than for the TM helices (page 179, column 2, last 9 lines), as in instant claim 1, lines 10-12.

23. The predicted structure has been outputted based on the all atom simulations (page 178, Figure 9), as in instant claim 1, lines 13-14.

24. Biggin et al. discloses in Table 1 the simulation of voltage gated K+ channel. It is well known in the art that voltage gated K+ channel is a type of G-protein coupled receptor (Voet & Voet, pages 1154 to 1155), as in instant claim 36.

25. Biggin et al. discloses simulations of helix/bilayer interactions usually employ a hydrophobicity index to represent the presence of a lipid bilayer (page 166, column 2, §6.1, Second paragraph). Biggin et al. discloses that inserting helices prefer to swing one end into the hydrophobic region, after first adopting a surface-bound orientation (page 167, column 2, last 5 lines), as in instant claims 38 and 44.

26. The predicted structure has been outputted based on the all atom simulations (page 178, Figure 9), as in instant claim 41.

27. These helices had evolved into a coiled-coil (loop) tetrametric structure with a left handed twist (page 172, column 1, lines 22-28). Fluctuations in the structure over the course of the simulation were greater for inter-helix loops than for the TM helices (page 179, column 2, last 9 lines), as in instant claim 42.

28. Simulations of N=5, 6, 7, and 8 bundles yielded stable (rigid) helix bundles (page 179, column 1, second paragraph), as in instant claim 45.

29. The simulation studies of Biggin et al. are directed to various solvent environments (page 171, column 1, lines 1-2), as in instant claim 46.

30. Biggin et al. discloses a mixed mode of molecular dynamics simulation comprising mean-field membrane simulations, all atom simulations, etc. discussed above, as in instant claim 48.

31. The simulation method of Biggin et al. comprises the approximation of a lipid bilayer as directed to free energy in a solution wherein the Poisson-Boltzman equation has been used to provide a continuum expression for the electrostatic potential due to the lipid headgroups and water (page 167, column 2), as in instant claims 51-54.

32. The simulation is performed for a time of (<10 ps) and (>100ps) (page 175, column 1, lines 6-8), as in instant claim 55.

33. Biggin et al. provides amino acid sequences for said membrane-bound proteins wherein bacteriorhodopsin has as set 7 helices comprising transmembrane regions. (page 169, Table 1), as in instant claims 56 and 57.

CLAIM REJECTIONS - 35 USC § 103

34. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

35. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

36. Claims 1, 3, 35-38, 41, 42, 44-46, 48, and 51-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Biggin et al. (1999) taken with Rose et al. (US 5680319 A).

RESPONSE TO ARGUMENT

37. Applicant's argument (pages 4-7) directed the Rose et al. and Kyte et al. has been full considered. Further, the claim amendments necessitated the withdrawal of the 35 U.S.C. 103(a) rejection as directed to Rose et al. and Kyte et al. has been withdrawn. The newly applied prior art rejection as directed to Biggin et al. (1999) taken with Rose et al. (US 5680319 A) has been necessitated by said claim amendments.

38. Biggin et al. discloses the limitations to claims 1, 36-38, 41, 42, 44-46, 48, and 51-57 as discussed above. Further, Biggin et al. discloses that it emerges that a major theoretical challenge is to exploit the results of all atom simulations in order to improve the mean field approach (Abstract etc.).

39. However, Biggin et al. does not disclose the limitation of claims 3 and 35.

40. Rose et al. discloses a computer-implemented simulation method for structure prediction based on the amino acid sequence within a fixed, sequential interval of allowed interaction, then repeats this process in stages as the interval size increases (Abstract etc. and column 3, lines 27-30).

41. During each cycle for 50-residue or greater fragments, a residue pointer is advanced sequentially from N to C. The bundle of helices is based on the canonical helices (one of four conformations) (untitled conformation table, columns 5-6). Upon completion, the minimum energy structure is among the ensemble of conformations from the final interval (column 5, lines 4-6), as in instant claims 3 and 35.

42. An artisan of ordinary skill in the art at the time of the instant invention would have been motivated by the improvement disclosed by Biggin et al. to improve the mean field approach for protein structure prediction as described by Rose et al. Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to use the computer-implemented of Biggin et al. and Rose et al. for predicting the structure of membrane-bound proteins.

43. Claims 1, 36-42, 44-46, and 48-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Biggin et al. (1999) taken with Mathiowetz et al. (1994).

44. Biggin et al. discloses the limitations to claims 1, 36-38, 41, 42, 44-46, 48, and 51-57 as discussed above. Further, Biggin et al. discloses that it emerges that a major theoretical challenge is to exploit the results of all atom simulations in order to improve the mean field approach (Abstract etc.).

45. However, Biggin et al. does not disclose the limitation of claims 39, 40, 49, and 50.

46. Mathiowetz et al. describes protein simulations techniques comprising the cell multiple method for nonbond interactions and the Newton-Euler Inverse Mass Operator (Abstract etc.), as in instant claims 39, 40, and 50.

47. Biggin et al. describes simulations of N=5, 6, 7, and 8 bundles yielded stable (rigid) helix bundles (page 179, column 1, second paragraph), as in instant claim 49.

48. An artisan of ordinary skill in the art at the time of the instant invention would have been motivated by the improvement disclosed by Biggin et al. to improve the mean field approach for protein structure prediction by using the protein simulations described by Mathiowetz et al. Therefore, it would have been obvious to one having ordinary skill in the art at the time

of the invention was made to use the computer-implemented of Biggin et al. and Mathiowetz et al. for predicting the structure of membrane-bound proteins via protein simulations.

49. Claims 1, 36-38, 41, 42, 44-48, and 50-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Biggin et al. (1999) taken with Mayo et al. (1990).

50. Biggin et al. discloses the limitations to claims 1, 36-38, 41, 42, 44-46, 48, and 50-57 as discussed above. Further, Biggin et al. discloses that it emerges that a major theoretical challenge is to exploit the results of all atom simulations in order to improve the mean field approach (Abstract etc.).

51. However, Biggin et al. does not disclose the limitation of claim 47.

52. Mayo et al. describes a method requiring new parameters, DREIDING, useful for predicting structures and dynamics of organic, biological, and main-group inorganic molecules (Abstract etc.), as in claim 47.

53. An artisan of ordinary skill in the art at the time of the instant invention would have been motivated by the improvement disclosed by Biggin et al. to improve the mean field approach for protein structure prediction by using the protein simulations described by Mayo et al. Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to use the computer-implemented of Biggin et al. and Mayo et al. for predicting the structure of membrane-bound proteins via DREIDING.

54. It is noted that the Mathiowetz et al. and Mayo et al. references are not provided in the instant Office Action because said references have been considered on FORM PTO-1449, filed March 08, 2004 and February 15, 2002, respectively.

CONCLUSION

55. The Lack of Enablement Under 35 U.S.C. § 112, First Paragraph has been withdrawn because Applicant's argument that "the applicant's predicted BRDP structure compares reasonably well with the crystallographic BRDP structure" has been found to be persuasive. Further, the specification discloses in Example 1 (page 19) "[s]tarting from the sequence..., and without using coordinates from the crystal structure." "Thus, the modeling...gives a reasonable structure as compared with the crystal structure for a known membrane protein." Applicant further demonstrates the claimed method with sequences without known crystal structures. Therefore, the use of crystal structure cited above has been reasonably as a confirmation of Applicant's invention, but the crystal structure is critical to the claimed invention.

56. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

57. Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic

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58. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

59. Any inquiry concerning this communication or earlier communications from the examiner should be directed to C. Dune Ly, whose telephone number is (571) 272-0716. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

60. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (571) 272-0722.

C. Dune Ly
1/8/05

MICHAEL P. WOODWARD
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JAN 09 2005